



# The Efficacy of Mirodenafil for Chronic Prostatitis/Chronic Pelvic Pain Syndrome in Middle-Aged Males

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**Purpose:** The aim of this study was to investigate the efficacy of mirodenafil in middle-aged male patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

**Materials and Methods:** Eighty-eight males with CP/CPPS were randomized to receive either levofloxacin (500 mg/d) (group L, 40 patients) or levofloxacin (500 mg/d) and mirodenafil (50 mg/d) (group ML, 48 patients) for six weeks. The International Prostate Symptom Score (IPSS), National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), and erectile function (EF) domain scores of the International Index of Erectile Function (IIEF) questionnaire were used to grade symptoms at baseline and 6 weeks after treatment.

**Results:** The mean change in total IPSS from baseline was higher in group ML than that in group L (group L, -1.1 vs. group ML, -4.3;  $p < 0.05$ ). Significant improvements were also seen in the IPSS voiding subscore (group L, -0.7 vs. group ML, -3.0;  $p < 0.05$ ). Changes observed in the NIH-CPSI of group ML at six weeks were greater than those at baseline (group L, -3.2 vs. group ML, -7.2;  $p < 0.05$ ). Significant improvements were seen in the NIH-CPSI voiding (group L, -0.5 vs. group ML, -1.7;  $p < 0.05$ ) and quality of life domains (group L, -1.0 vs. group ML, -1.8;  $p < 0.05$ ). Group ML showed a significantly greater increase in the IIEF-EF score than did group L (group L, +0.2 vs. group ML, +7.8;  $p < 0.05$ ).

**Conclusions:** Mirodenafil (50 mg once daily) was well tolerated and resulted in significant symptomatic improvement in middle-aged males with CP/CPPS.

**Key Words:** Chronic prostatitis with chronic pelvic pain syndrome; Erectile dysfunction; Phosphodiesterase 5 inhibitors; Treatment outcome

## INTRODUCTION

The United States National Institutes of Health (NIH) International Collaborative Prostatitis Network developed a prostatitis classification system in 1995. The most com-

mon type of prostatitis is category III, or chronic prostatitis. The definition of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) includes genitourinary pain with or without voiding symptoms in the absence of uropathogenic bacteria, as detected by standard microbiological

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methods, or another identifiable cause such as malignancy [1]. CP/CPPS is a highly prevalent condition affecting males of a wide age range, but its etiology remains unclear. Lifetime CP/CPPS prevalence is 2% to 10% [2]. Many etiologies and mechanisms for CP/CPPS pathogenesis have been proposed, including infection, detrusor-sphincter dysfunction, immunological dysfunction, interstitial cystitis, and neuropathic pain [3]. The efficacy of various medical therapies, such as antibiotics, alpha-adrenergic blockers, anti-inflammatory agents, hormonal therapies, and phytotherapies, has been evaluated in clinical studies of CPPS [2,4,5]. However, evidence is lacking or conflicting [6]. Among these therapies, alpha-adrenergic antagonists provide symptomatic relief for some patients with CP/CPPS. The mechanism by which alpha-blockers relieve lower urinary tract symptoms (LUTS) in patients with CP/CPPS involves smooth muscle relaxation of the bladder neck and prostate due to alpha-adrenergic blockade, leading to increased urinary flow and decreased urinary retention [7]. Both nitric oxide synthase and phosphodiesterase-5 (PDE-5) are present in human prostatic tissue. Many studies have shown that PDE-5 inhibitors improve LUTS through several mechanisms. Urinary reflux into prostatic ducts has been suggested as a mechanism of CP [8]. The results of nitric oxide donors and PDE-5 inhibitors in *in vitro* studies indicate that PDE-5 inhibitors relax prostatic smooth muscle, which increases the washout of prostatic reflux products and reduces prostatic inflammation and consequent prostatitis symptoms [8,9]. We postulate that mirodenafil, a newly developed PDE-5 inhibitor, may relieve prostatitis symptoms.

## MATERIALS AND METHODS

### 1. Study design

Eighty-eight males with CP/CPPS were randomized in a single-blind fashion to receive either levofloxacin (500 mg once daily, group L, 40 patients) or levofloxacin (500 mg once daily) and mirodenafil (50 mg once daily, group ML, 48 patients) for six weeks. Approval for this study was obtained from the Institutional Review Board of Pusan National University Hospital.

### 2. Subjects

The diagnostic evaluation of CP/CPPS included a detailed history and physical examination, transrectal ultrasonography, urine flow measurements, residual urine volume measurements, standard microbiological cultures, and a urinalysis. Expressed prostatic secretions were analyzed if available. Patients included in the study fulfilled the requirements for NIH category III CP/CPPS [1]. Exclusion criteria included symptoms for <three months, proven urinary tract infection, invasive prostate-related procedures (transurethral resection of the prostate, transurethral incision of the prostate, or transurethral needle ablation), LUTS without significant pain, significant signs and symptoms of obstructive voiding, or prostate volume of  $>50 \text{ cm}^3$ .

### 3. Outcome measurements

The International Prostate Symptom Score (IPSS), NIH Chronic Prostatitis Symptom Index (NIH-CPSI), and erectile function (EF) domain scores of the International Index of Erectile Function (IIEF) questionnaire were used to grade symptoms at baseline and after six weeks of treatment.

### 4. Statistical analysis

All variables were compared between the groups at the end of the six-week treatment arm. Data are presented as means  $\pm$  standard deviations. The baseline characteristics of the two groups were assessed using the Mann-Whitney U test. Changes from baseline within each group were assessed using repeated-measures analysis of variance (ANOVA). Two-way ANOVA was performed to evaluate the interaction between levofloxacin and mirodenafil. Statistical analyses were performed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). A value of  $p < 0.05$  was considered statistically significant.

## RESULTS

The mean ages of the two groups were  $44.2 \pm 6.9$  and  $45.3 \pm 7.0$  years, respectively. No differences were observed between groups L and ML in terms of age, prostate volume, prostate-specific antigen level, maximum urinary

flow rate, residual urine volume, or symptom duration. The IPSS, NIH-CPSI, and IIEF-EF domain scores were the same in both groups at baseline (Table 1). Mirodenafil significantly improved the mean change in IPSS from baseline at six weeks (group L,  $-1.1$  vs. group ML,  $-4.3$ ;  $p < 0.05$ ) (Table 2). Significant improvements were also seen in the IPSS voiding subscore (group L,  $-0.7$  vs. group ML,  $-3.0$ ;  $p < 0.05$ ). Changes from baseline in the NIH-CPSI at six weeks observed in group ML were greater than those in group L (group L,  $-3.2$  vs. group ML,  $-7.2$ ;  $p < 0.05$ ). Significant improvements were also seen in the NIH-CPSI voiding score (group L,  $-0.5$  vs. group ML,  $-1.7$ ;  $p < 0.05$ ) and the quality of life (QoL) domains

**Table 1.** Baseline characteristics

Patient characteristic	Group L (n=40)	Group ML (n=48)
Age (yr)	44.2±6.9	45.3±7.0
Prostate volume (cm <sup>3</sup> )	33.0±5.4	34.0±5.5
Prostate-specific antigen (ng/mL)	1.2±0.5	1.4±0.7
Maximum urinary flow rate (mL/s)	14.0±4.2	15.0±5.1
Residual urine volume (mL)	20.0±6.4	21.0±6.1
Symptom duration (mo)	19.2±3.9	21.5±4.5

Values are presented as mean±standard deviation.

Group L: levofloxacin group, Group ML: mirodenafil+levofloxacin group.

**Table 2.** Changes in the IPSS from baseline to 6 weeks

Variable	IPSS	
	Baseline	Changes from baseline to 6 weeks
Group L (n=40)		
Total	12.0±1.2	-1.1±0.2
Storage	3.9±0.4	-0.4±0.1
Voiding	8.1±0.5	-0.7±0.1
QoL	3.6±0.3	-0.1±0.1
Group ML (n=48)		
Total	14.1±1.0	-4.3±0.2*
Storage	4.9±0.4	-1.3±0.1
Voiding	9.2±0.6	-3.0±0.2*
QoL	3.3±0.3	-0.2±0.1*

Values are presented as mean±standard deviation.

IPSS: International Prostate Symptom Score, QoL: quality of life, Group L: levofloxacin group, Group ML: mirodenafil+levofloxacin group.

\*Significant difference compared to group L ( $p < 0.05$ ).

(group L,  $-1.0$  vs. group ML,  $-1.8$ ;  $p < 0.05$ ) (Table 3). Group ML showed a significantly greater increase in the IIEF-EF score than group L (group L,  $+0.2$  vs. group ML,  $+7.8$ ;  $p < 0.05$ ) (Table 4). No significant change from baseline to the end of treatment and no significant difference in maximum urinary flow rate or mean residual urine volume were observed between the two groups (Table 5, 6). No significant levofloxacin-mirodenafil interaction was detected. Commonly reported ( $\geq 1$  case) adverse treatment events in group ML were frequent erections, dyspepsia, and headache (each,  $\leq 2$  cases); however, no patient discontinued treatment due to adverse events.

**Table 3.** Changes in the NIH-CPSI from baseline to 6 weeks

Variable	NIH-CPSI	
	Baseline	Changes from baseline to 6 weeks
Group L (n=40)		
Total	22.1±1.5	-3.2±0.2
Pain	10.5±0.5	-1.7±0.1
Urinary	4.2±0.4	-0.5±0.2
QoL	7.4±0.5	-1.0±0.2
Group ML (n=48)		
Total	19.5±1.6	-7.2±0.1*
Pain	7.9±0.4	-3.7±0.1
Urinary	4.4±0.5	-1.7±0.1*
QoL	7.2±0.5	-1.8±0.1*

Values are presented as mean±standard deviation.

NIH-CPSI: NIH-Chronic Prostatitis Symptom Index, QoL: quality of life, Group L: levofloxacin group, Group ML: mirodenafil+levofloxacin group.

\*Significant difference compared to group L ( $p < 0.05$ ).

**Table 4.** Changes in the IIEF-EF from baseline to six weeks

Variable	IIEF-EF	
	Baseline	Changes from baseline to 6 weeks
Group L (n=40), total	18.8±6.2	0.2±2.4
Group ML (n=48), total	18.2±6.0	7.8±1.8*

Values are presented as mean±standard deviation.

IIEF-EF: International Index of Erectile Function-Erectile Function, Group L: levofloxacin group, Group ML: mirodenafil+levofloxacin group.

\*Significant difference compared to group L ( $p < 0.05$ ).

**Table 5.** Changes in mean maximum urinary flow rate pre- and post-treatment from baseline to six weeks

Variable	Mean maximum urinary flow rate (mL/s)	
	Baseline	Changes from baseline to 6 weeks
Group L (n=40)	14.0±4.2	1.1±2.1
Group ML (n=48)	15.0±5.1	-0.7±0.3

Values are presented as mean±standard deviation.  
Group L: levofloxacin group, Group ML: mirodenafil+levofloxacin group.

## DISCUSSION

The most recent NIH classification of prostatitis adopted in 1995 includes several clinical entities, such as acute and chronic bacterial infections, CPPS, and asymptomatic inflammation of the prostate. The most common type of prostatitis is category III, also known as CP. The current NIH definition of CP/CPPS includes genitourinary pain with or without voiding symptoms in the absence of uropathogenic bacteria, as detected by standard microbiological methods, or another identifiable cause such as malignancy [1,4]. The efficacy of various medical therapies, such as antibiotics, alpha-adrenergic blockers, anti-inflammatory agents, hormonal therapies, and phytotherapies, has been evaluated clinically [2,4,5]. However, evidence is lacking or conflicting [6]. Several reports have suggested that PDE-5 inhibitors improve LUTS. Chung et al [10] showed that a PDE-5 inhibitor improved IPSS and IIEF scores as well as Qmax compared with placebo. LUTS is one of the main symptoms in patients with CP/CPPS. The mechanism includes expression and wide distribution of nitric oxide/cyclic guanosine monophosphate/PDE-5 pathway components in the human lower urinary tract and supports involvement of this pathway. In particular, PDE-5 inhibitors regulate smooth muscle activity in these organs. Increased smooth muscle tension plays a central role in LUTS pathophysiology, and very commonly prescribed medications, such as alpha-adrenergic blockers and antimuscarinics, relax smooth muscle in either the prostate or the bladder [11]. We speculated that mirodenafil would improve CP/CPPS symptoms. Our results show that a six-week mirodenafil treatment significantly improved total and voiding volumes, as well as

**Table 6.** Changes in mean residual urine volume pre- and post-treatment from baseline to 6 weeks

Variable	Mean residual urine volume (mL)	
	Baseline	Changes from baseline to 6 weeks
Group L (n=40)	20.0±6.4	1.2±0.8
Group ML (n=48)	21.0±6.1	-1.7±0.3

Values are presented as mean±standard deviation.  
Group L: levofloxacin group, Group ML: mirodenafil+levofloxacin group.

QoL on the IPSS. These findings are consistent with results from previous studies revealing the effect of mirodenafil on LUTS [10,12,13]. However, to the best of our knowledge, thus far, no study has evaluated the efficacy of PDE-5 inhibitors in patients with CP/CPPS, and there has been no controlled human clinical study on the effect of PDE-5 inhibitors in patients with CP/CPPS. Thus, our study is the first human trial to evaluate the therapeutic effects of a PDE-5 inhibitor on CP/CPPS. In this study, mirodenafil significantly improved the total, urinary, and QoL domains, but no change in the pain scale was detected. Thus, we concluded that the effect of mirodenafil on CP/CPPS mainly depended on the improvement in LUTS, because LUTS is the main symptom in patients with CP/CPPS.

Mirodenafil is a newly developed pyrrolopyrimidinone compound and a potent selective oral PDE-5 inhibitor [14,15]. Mirodenafil was launched in Korea in 2007, and an orally disintegrating mirodenafil film was developed in 2011 for patients who have difficulty swallowing tablets [16]. The Tmax and T1/2 values of mirodenafil are 1.25 hours and 2.5 hours, respectively [17]. Preclinical studies have revealed that the selectivity of mirodenafil to PDE-5 is 10-fold higher than that of sildenafil, whereas the inhibitory effects of mirodenafil on other PDEs are lower than those of sildenafil [18]. One study showed that mirodenafil significantly improves erectile dysfunction (ED) and is well tolerated in a representative population of Korean males with broad-spectrum ED of various etiologies and severities [14].

In our study, mirodenafil significantly increased the IIEF-EF domain by  $7.8 \pm 1.8$ ; however, no changes in maximal urinary flow rate or mean residual urine volume were observed. These findings are consistent with those of Lee

et al [12]. However, two studies reported improvements in Qmax after mirodenafil treatment [10,13]. This inconsistency in the effect of mirodenafil on urinary flow rate is similar to that of other PDE-5 inhibitors, such as tadalafil [18]. The variable urinary flow rate results after treatment with a PDE-5 inhibitor may be due to the diverse baseline characteristics of the enrolled patients.

Several limitations of this study should be noted. Although we identified significant improvements in IPSS and NIH-CPSI after mirodenafil treatment, we found no change in pain or storage symptoms. Further studies to assess these parameters will enhance our understanding of the mechanism of action of mirodenafil in patients with CP/CPPS. In addition, the number of patients and the treatment duration were insufficient to elucidate the effects of mirodenafil on CP/CPPS. Finally, this study was not double blinded, and no placebo treatment arm was included.

## CONCLUSIONS

Although mirodenafil did not improve all CP/CPPS domains, a six-week treatment of mirodenafil (50 mg) once daily was well tolerated by and resulted in significant symptomatic improvement in middle-aged males with CP/CPPS. This result indicates that mirodenafil may be a useful agent for the treatment of CP/CPPS as monotherapy or combination therapy with other empirical drugs. Future studies to establish the mechanism and effect of treatment are needed.

## ACKNOWLEDGEMENTS

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